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Biomarkers of oxidative stress in cardiopulmonary medicine

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Document Version

Publisher's PDF, also known as Version of record

Publication date:

2007

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gerritsen, W. B. M. (2007). *Biomarkers of oxidative stress in cardiopulmonary medicine*. [Thesis fully internal (DIV), University of Groningen]. [s.n.].

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Summary

Ischemia as well as oxidative stress occurs common during coronary artery bypass grafting (CABG). The purines hypoxanthine, xanthine and uric acid as markers of ischemia, and malondialdehyde as a marker of oxidative stress, are useful biomarkers giving a good impression of the damage caused during CABG.

In chapter 1 the background of the thesis was described. In this thesis we focus on CABG and chronic obstructive pulmonary disease (COPD). Aspects such as ischemia, oxidative stress, reactive oxygen species, lipid peroxidation, and antioxidants were described.

In chapter 2 biomarkers and their usefulness in clinical practice were reviewed. Hypoxanthine, xanthine, uric acid and malondialdehyde were selected as markers of ischemia and oxidative stress to get a good impression of oxidative stress that was released during CABG using different surgical techniques. For COPD, hydrogen peroxide in exhaled breath condensate was chosen as an early noninvasive marker to detect and monitor the inflammatory process of the lung.

In chapter 3, the aim and outline of the thesis was described.

In chapter 4 indices of oxidative stress were measured in urine as well as in serum. Additionally the clearance of malondialdehyde, hypoxanthine, xanthine and uric acid by the kidney before, during and after CABG were discussed. Their concentrations were expressed as ratio of the urinary creatinine to correct for changes in renal function due to the surgical procedure. The excretion of the purines, hypoxanthine, xanthine and uric acid was still increased during CABG despite correction for creatinine. The increase of the concentrations of purines and malondialdehyde indicates global oxidative tissue injury by reactive oxygen species.

In chapter 5 the difference in oxidative stress and the effect on renal function by on-pump versus off-pump CABG before, during and after the intervention was

shown. The results indicated that patients undergoing off-pump CABG had only mild signs of oxidative stress compared to on-pump CABG. Furthermore, renal function expressed by creatinine clearance remained nearly constant for the off-pump group as compared to the on-pump group, in which the renal function during the surgery significantly decreased and only slowly recovered.

In chapter 6 malondialdehyde and uric acid in serum were measured during CABG using three different surgical techniques: mini extra corporeal circuit, conventional and off-pump CABG. We found significant lower levels of malondialdehyde in favour of the off-pump group. Thereby, only mild ischemia and oxidative stress in patients undergoing off-pump or mini CABG was found as compared to conventional CABG.

Airway inflammation plays an important role in various respiratory lung diseases, including chronic obstructive pulmonary disease (COPD). The progression of COPD is associated with increasing frequency and severity of exacerbations. In addition, it is linked to poor health status and can be life threatening, particularly in patients with advanced disease.

Therefore several attempts have been made to detect and monitor inflammatory changes using non-invasive methods. The marker hydrogen peroxide in exhaled breath condensate (EBC) proved to be informative and gave a good impression of the severity of airway inflammation.

In chapter 7, patients with an exacerbation of COPD, the following biomarkers were monitored: hydrogen peroxide in EBC, IL-8, sICAM and sE-selectin during treatment with prednisolone. Increased levels of oxidative stress and inflammation were noticed in the airways of the patients admitted to the hospital because of exacerbation of COPD. During treatment with prednisolone both hydrogen peroxide in EBC and sICAM in serum decreased.

In chapter 8 we performed a study regarding the priming status of neutrophils during an exacerbation of COPD and during resolution of this clinical condition. To determine whether inflammation-associated priming of neutrophils in the peripheral blood was accompanied by a change in a tissue associated inflammatory marker, hydrogenperoxide in EBC was measured. We demonstrated that systemic neutrophil preactivation is increased during an exacerbation of COPD and that local inflammation induced an activation of the systemic immune system. In conclusion, primed neutrophils can be found in peripheral blood during an exacerbation of COPD. Upon treatment of the exacerbation priming of neutrophils as well as the hydrogenperoxide concentration decreased. These observations suggest that the expression of priming associated markers in peripheral neutrophils may be used as read out for the inflammatory processes in COPD.

In chapter 9, we discussed the results of the level of oxidative stress by measuring hydrogen peroxide concentration in EBC. Unfortunately the methods to measure hydrogen peroxide are all rather time consuming and only reliable and accurate in the hands of a skilled technician in a dedicated laboratory. We tested a new commercial device (EcocheckTM), developed to offer a less time-consuming method to measure hydrogen peroxide. The preliminary validation of the instrument/method was performed according to the NCCLS EP10-A2 protocol. Further evaluation should be done by measuring more patients and compare these results with other accepted methods. Results were acceptable, however a part of criticism was still that there is no quality check to control the biosensors for deviates in day-to-day reproducibility. Furthermore, the EcocheckTM is “an easy to use” measuring device for obtaining quick results and can be used by non-skilled technicians to determine hydrogen peroxide concentrations.

Conclusions

We investigated hypoxanthine, xanthine, uric acid and malondialdehyde in patients undergoing CABG using three different surgical techniques for CABG. Also we monitored oxidative stress and inflammation in the lungs of patients with exacerbated COPD by means of several biomarkers.

We found that ischemia and oxidative stress is minimal in patients using the mini extra corporeal circuit and the "Octopus" off-pump CABG when compared to the conventional on-pump CABG technique. Thereby, using off-pump CABG, renal function did not change significantly. Therefore, we conclude that the off-pump CABG technique can be a good alternative for patients undergoing CABG with renal dysfunction.

Patients admitted at the hospital with an exacerbation of COPD had all strongly increased levels of hydrogen peroxide in EBC. Inflammation of the lungs as measured in blood with the biomarkers s-ICAM and priming associated markers of peripheral neutrophils, decreases during treatment with prednisolone even as hydrogen peroxide in EBC. However treatment with prednisolone of the patients is standardized and continued until the patient feels better. Unfortunately, it's still possible that the inflammation in the lungs is still ongoing after the treatment is stopped. Most of these patients will re-exacerbate within a short period after discharge from the hospital. We conclude that hydrogen peroxide in EBC is a reliable, early non-invasive biomarker that reflects ongoing inflammation in the lungs.